

# Generation of Dimethylnitrosamine in Water Purification Systems

## Detection in Human Blood Samples During Hemodialysis

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• Dimethylnitrosamine (DMNA), a carcinogen, was detected at levels up to 32  $\mu\text{g/L}$  in dialysate from five of 16 dialysis units surveyed. Blood drawn from patients at one of these units in which DMNA was raised in the dialysate showed a significant increase in the amount of DMNA in the patient's blood when predialysis levels were compared with 15-minute intradialysis levels. The presence of a mixed-bed deionizer without an antecedent carbon filter appeared to be necessary for DMNA production. These data suggest that DMNA is generated in certain water purification systems and may then diffuse into the patient's blood. Guidelines for deionizer-treated water should be revised to include an activated carbon filter.

(JAMA 1983;250:2020-2024)

DIMETHYLAMINE (DMA), a precursor of the potent carcinogen dimethylnitrosamine (DMNA), is present in the blood and small intestine of patients with end-stage kidney failure, including patients undergoing long-term dialysis.<sup>1</sup> These findings are associated with bacterial overgrowth of the small intestine.<sup>2</sup> It was postulated that generation of amines, particularly DMA, might occur locally as a result of intestinal bacterial metabolism. Because of the presence of an active precursor and reports

suggesting an increased incidence of cancer in chronic renal failure,<sup>3</sup> we investigated the possibility of in vivo formation of DMNA in uremic patients. As part of this investigation, to exclude exogenous sources of the substrate DMA or preformed DMNA, we examined water obtained from treatment systems at several dialysis units in the Pennsylvania, Delaware, and New Jersey areas for the presence of volatile nitrosamines. We found DMNA in dialysate of some of the units tested, although its appearance was unanticipated. Its presence, however, clearly has important implications in water purification systems in general; our study was focused on this aspect rather than on in vivo DMNA formation.

### PATIENTS AND METHODS

Patients were randomly selected by the attending physicians at the respective dialysis units with the restriction that anephric and hepatitis B-positive patients

were excluded. All patients were chronically ill and had been undergoing dialysis three times per week for at least one year. Patients were required to be informed of our research protocol, and their permission was obtained. Some of those who were selected refused to have their blood collected, and some who originally let us take predialysis blood samples refused to allow us to take further blood samples.

### Evaluation of Processing Systems Among Dialysis Units

Municipal tap water, deionized water used to make dialysate, commercial dialysate concentrates, and blood samples from patients were assayed for DMNA. The water was sampled and assayed before treatment (municipal tap water) and again after its constitution as final dialysate before its use in the dialyzer. Sequential processing of municipal tap water through various purification steps varies from one dialysis unit to another, depending on the initial water purity profile. Possible purification steps are illustrated in the Figure, but the actual purification steps for each of the 16 dialysis units eventually studied are presented in Table 1. Following the purification step(s), the water was mixed with concentrate containing the physiological profile of the electrolyte patterns in the blood. The Figure indicates the collection sites at various points in the system, before, during, and after water treatment.

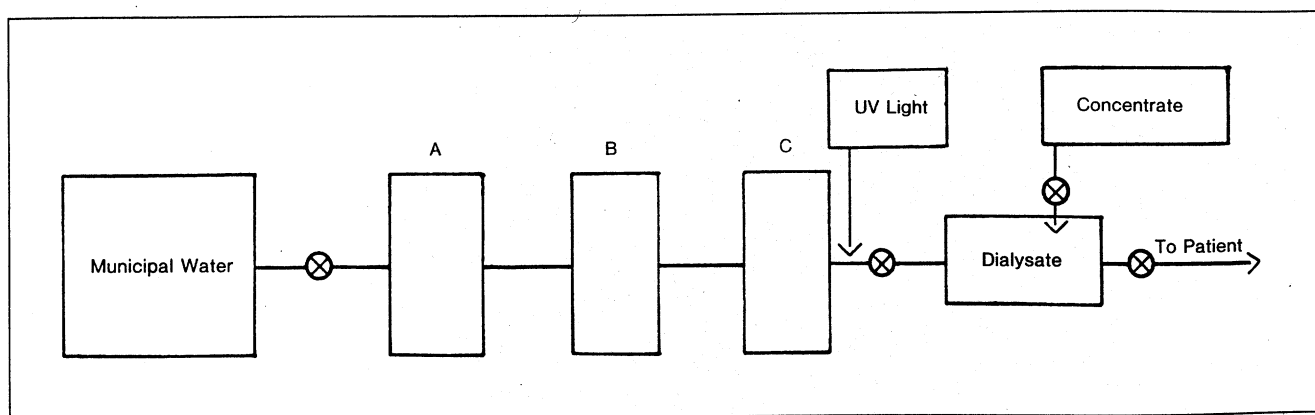
### Collection of Water and Blood Specimens

After finding high DMNA levels in the water at one unit, we decided to survey as many other units in the area as we could. Dialysate from 16 different units was

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Read in part before the Association for the Advancement of Medical Instrumentation, Washington, DC, Jan 29, 1981, and presented as a poster at the meeting of the American Society of Nephrology, Washington, DC, Nov 23, 1980.

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Possible water purification steps.

Table 1.—Distribution of Water Treatment Modules

Order of Water Treatment System Components*					Presence of Dimethylnitrosamine
Unit	1	2	3	4	
Group 1					
1-2	Water softener†	...	...	...	—
3	Sand	Water softener‡	Reverse osmosis	...	—
4	Membrane filter	Carbon	...	...	—
5	None	...	...	...	—
6	Reverse osmosis	...	...	...	—
7, 8	Carbon	Deionizer	UV light	...	—
9, 10	Deionizer	UV light	...	...	—
11	UV light	Carbon	Reverse osmosis	Deionizer	—
Group 2					
12	Deonizer	...	...	...	+++
13§	Sand	Reverse osmosis	Deionizer	...	+++
14-16	Deionizer	...	...	...	+

\*Numbers in these columns refer to the order in which each module is connected from the entry of municipal water to emergence of final dialysate. Note that no dimethylnitrosamine (DMNA) was formed if there was an activated carbon (charcoal) filter before the deionizer or a UV light after the deionizer, or both.

†Separate cation-exchange resin to remove  $\text{Ca}^{++}$   $\text{Mg}^{++}$ .

‡Separate cation exchange resin for  $\text{Ca}^{++}$   $\text{Mg}^{++}$  removal, followed by anion-exchange "dealkalizer" necessary before reverse osmosis.

§Unit 13, which was strongly positive for DMNA, was later modified by placing an activated carbon filter before the deionizer. The result was disappearance of DMNA from dialysate.

obtained and assayed for DMNA. This was not a prospectively designed study. The dialysis units were retrospectively divided into two groups according to levels of DMNA subsequently found (Table 1). Group 1 consisted of units in which dialysate showed no detectable ( $<0.05 \mu\text{g/L}$ ) DMNA. Group 2 had measurable ( $>0.05 \mu\text{g/L}$ ) DMNA levels. Dialysate samples were obtained from each of 11 dialysis units in group 1 on two separate dates, for a total of 22 samples. Blood was collected from patients at four of these 11 units. Some units supplied predialysis blood samples, some 15-minute intradialysis samples, and some postdialysis samples. Since there was no DMNA in any of the dialysate from these units and blood DMNA levels were not substantially elevated, we could not justify more extensive blood sampling in this group. It was difficult to persuade patients to give 50 to 150 mL of blood repeatedly, and almost

impossible to obtain blood from patients at units with which our group had no true affiliation.

Group 2 dialysate samples were obtained from five separate units. One was a backup unit that was not in daily operation; four units were in daily operation. One of these four units (unit 13, Table 1) was an affiliate (this unit supplied all the group 2 patients' blood samples). Dialysate samples were collected from the affiliate unit on 13 separate dates (seven of which corresponded to when blood samples were drawn). The level of DMNA in the dialysate was monitored until the problem was resolved (approximately six months). Nine patients from this unit were randomly selected, and blood was drawn at three time periods. Compliance was easier in this group, since the benefit-risk ratio was higher and the patients knew of our concern. We were not successful in collecting any blood from people who

underwent dialysis at any unit from group 2 except our affiliate. There was no direct relationship between the number of dialysate samples tested in a unit and the number of blood samples examined. Dialysate was often tested on days when blood samples were not drawn. On days when blood samples were drawn, dialysate was always tested.

Predialysis blood specimens from patients were drawn directly from the arterial line before starting dialysis. Blood was drawn into a standard 50-mL plastic disposable syringe. The blood was immediately transferred to a 50-mL polypropylene centrifuge tube. Blood was protected from sunlight and fluorescent light to prevent nitrosamine photodecomposition then placed in either refrigerator or freezer until all blood samples were collected. Fifteen minutes after dialysis began, blood samples were collected from the arterial line (going from patient to dialyzer) by the same technique. Postdialysis blood samples were collected in the same way immediately at the end of dialysis. Blood specimens were either processed immediately or frozen until ready for use. Storage experiments conducted on blood with either spiked or normally present DMNA showed that DMNA was stable for at least eight days if frozen. All blood-carrying lines, syringes, and containers were analyzed and found to be negative for interfering peaks. Commercial blood-collecting tubes were not used because of reports that some tubes have contained nitrosamines.

#### Analysis of Water and Blood Specimens

Municipal tap water, deionized water, dialysate concentrates, and dialysate were collected directly into sterile 50-mL polypropylene centrifuge tubes. These tubes had been tested for the presence of volatile nitrosamines and found to be negative. An accurately weighed specimen (20.0 to 50.0 g) of one of these solutions was placed in a 250-mL separation funnel; 10 g of NaCl

was added. This solution was extracted three times with separate 80-mL volumes of dichloromethane (DCM). The extracts were combined and washed once with 50 mL of 6N HCl, then once with 50 mL of 5N NaOH. The DCM extract was then passed through 35 g of granular anhydrous Na<sub>2</sub>SO<sub>4</sub> held in a 60-mL coarse, fritted-glass funnel and collected into a 500-mL evaporative concentrator evaporator fitted with a 4-mL concentrator tube. The volume of the DCM extract was reduced to approximately 4 mL by means of a steam bath. Further reduction of the DCM extract to 1.0 mL was achieved using a microevaporative concentrator and a 65 °C water bath. An aliquot (7 to 9 µL) from the DCM extract was injected into a gas chromatograph (GC) interfaced with a chemiluminescent detector, an extremely sensitive and reportedly specific detector for nitrosamines. The presence of DMNA in the samples was determined by comparing the retention time of the suspected DMNA in the sample with the retention time of a pure DMNA standard that was injected at various times during the day. The DMNA was quantified by peak height analysis, using a calibrated external standard.

Blood was processed in a similar fashion. An accurately weighed specimen of blood (20.0 to 50.0 g) was transferred to a 1-L single-neck flask. Added to the flask were a few boiling chips, 50 mL of "nitrosamine-free" distilled deionized water, 30 mL of 1N NaOH, and 8 g of Ba(OH)<sub>2</sub>·8 H<sub>2</sub>O. An internal standard of methylethyl nitrosamine (MENA) (1.00 mL of 0.02 mg/L in DCM) was added to enable us to monitor recovery. The flask was set up for distillation at atmospheric pressure, using grease-free standard tapered glassware. Heat was supplied from a mantle connected to a variable transformer. Aqueous distillate was collected until the distillation flask became dry. The aqueous distillate was treated exactly as were the previously described water specimens.

#### Conditions for Analysis by GC-Chemiluminescence

The GC column was made from stainless steel, 2.7 m long with a 3.2-mm external diameter and packed with 15% polyethylene glycol (average molecular weight, 15,000 to 20,000) terminated with terephthalic acid on 60/80-mesh diatomaceous earth support. The carrier gas was helium at 35 mL/min. The column temperature for most analysis was programmed from 120 to 220 °C at 4 °C/min. This temperature program permitted analysis of many volatile nitrosamines. When only DMNA was being assayed, the column was run isothermally at 140 °C. The chemiluminescence detector furnace temperature was 450 °C, and the cold trap was liquid nitro-

Table 2.—Dimethylnitrosamine (DMNA) Levels in Dialysate and Blood in Nine Patients in Unit 13

Patient	Date	Dialysate*	DMNA, µg/L		
			Blood		
			Before Dialysis	15 min After Starting Dialysis	Immediately After Dialysis
1	1/14	21.0	0.05	1.46	...†
2	1/15	18.6	0.05	...†	1.25
3	1/23	7.60	0.05	1.15	0.35
4	4/16 (AM)	14.7	0.15	0.95	2.12‡
5	4/16 (PM)	13.8	0.16	1.40	1.49
6	6/25 (AM)	5.27	0.05	0.48	0.22
7	6/25 (PM)	2.86	0.10	0.62	0.29
8	6/26	3.85	0.16	0.63	0.41
9	7/03	1.44	0.15	0.66	0.14
Mean ± SD§			0.12 ± 0.05	0.84 ± 0.36	0.72 ± 0.77

\*Dimethylnitrosamine in dialysate was measured at start of dialysis. The level was ± 2 µg/kg within the day, but varied from day to day because of changes made in water treatment system.

†Sample not collected.

‡This value appears to be high compared with the trend. We have no reason to suspect a determinant error. It may be a result of slower metabolism since this patient had impaired liver function.

§For purposes of comparison, mean DMNA blood levels are shown for patients 3 through 9, omitting patients 1 and 2 because of incomplete collections.

gen/ethanol slurry (−115 °C). These conditions permitted quantitative reproducible analysis of DMNA at levels below micrograms per liters.

#### Confirmation of DMNA-Positive Peaks in Water and Blood Specimens

**Photolytic Technique.**—Eighty-nine percent of all the samples positive for DMNA by GC-TEA were presumptively confirmed by UV photolysis. Highly colored samples were not photolizable directly and had to be cleaned up using an acid-treated diatomaceous earth column before being subjected to this confirmation procedure.

**Mass Spectrometry (MS) Technique.**—Blood and dialysate extracts in which sufficient DMNA was present (by chemiluminescence) were subjected to either high- or low-resolution MS for confirmation. Fifty-three percent of the DMNA-positive samples had sufficient amounts of DMNA for MS confirmation. Each sample had to contain more than 70 ng before cleanup. Initially, similar samples were pooled to lessen the number of GC-MS analyses, since the GC-MS equipment was shared by a number of laboratories. Five pooled dialysate samples, representing 17 separate specimens, were confirmed by low-resolution GC-MS, as described by Kimoto et al.<sup>4</sup> For this procedure, three ions, with mass-charge ratios of 30, 42, and 74, were monitored; their presence before and their absence after photolysis under UV light were considered confirmatory evidence of their presence. Pooled samples for analysis by low-resolution GC-MS underwent a cleanup procedure on a silicic acid column (deactivated with 5% water). The column was washed with 50 mL of DCM in *n*-

pentane (4:10) and eluted with 50 mL of DCM. The eluate was concentrated to approximately 1 mL in an evaporative concentrator apparatus on a steam bath, and then to 20 to 100 µL under partial vacuum. The concentrate was sealed in two capillary tubes. One tube was photolyzed at 365 nm for three hours. Both were analyzed by the low-resolution GC-MS as already described. Four pooled samples, representing six blood specimens and two dialysate samples, were confirmed by high-resolution GC-MS. All samples sent for MS were positive for DMNA.

#### Statistical Methods

Fisher's exact test was used to determine whether the appearance of DMNA in the initial dialysate sample obtained from a unit was related to use by that unit of a mixed-bed deionizer unmodified by a carbon filter or UV light. In one unit in which DMNA was consistently found in dialysate, blood was drawn from nine different patients at three time periods (before dialysis, 15 minutes after starting dialysis, and immediately after dialysis) on seven different days. Simple linear regression was performed to determine if a relationship existed between levels of DMNA in dialysate and the levels of DMNA in blood at the respective time periods. Two blood collections were unfortunately omitted (patient 1 after dialysis and patient 2 fifteen minutes after starting dialysis [Table 2]). Single-factor analysis of variance with repeated measurements was performed to determine whether a difference existed between DMNA blood levels before, 15 minutes after starting, and after dialysis for the nine patients at one unit from group 2 (Table 2).

## RESULTS

Experiments to determine recovery and reproducibility of analysis of DMNA at low levels in both water samples and blood specimens were performed. Recovery of DMNA and MENA from water samples showed excess of 98% for both. Recovery of added internal standard of MENA in blood specimens was  $94\% \pm 5\%$ . The analysis of DMNA in whole blood at the levels and conditions reported in this article were very reproducible. Ten replicate analyses of a DMNA-spiked blood specimen showed a mean concentration of  $0.3 \mu\text{g/L}$ , with an SD of  $0.1 \mu\text{g/L}$ .

The dialysis units were retrospectively grouped into groups 1 and 2 according to the presence or absence of DMNA in the dialysate (minimum detectable limit,  $0.05 \mu\text{g/L}$ ). Thus, no DMNA was detected, as defined, in the 11 units from group 1, and DMNA was detected in the dialysate from all five units from group 2. Two of these five units had very high DMNA levels (mean,  $13 \mu\text{g/L}$ ), and three had concentrations of DMNA that were moderately raised (mean,  $0.62 \mu\text{g/L}$ ). Dimethylnitrosamine, however, was not detected in any municipal tap water or commercial dialysate concentrates.

Predialysis blood samples were collected from ten patients at one unit (unit 11) in which DMNA was not present in the dialysate (group 1). These samples were collected on three separate days over a six-day period. All blood DMNA levels were below the detectable limit ( $0.05 \mu\text{g/L}$ ), except for one patient in whom DMNA was found to be only slightly raised to  $0.08 \mu\text{g/L}$  (a very low level not significantly different from  $0.05 \mu\text{g/L}$ ).

Predialysis blood samples were also collected from nine patients at a different unit (unit 13) in which DMNA was present in the dialysate (group 2, Table 2). The blood was collected on seven separate dates over a six-month period. Table 2 shows the results in the nine patients of unit 13 (group 2). Five of the nine had very low but detectable ( $\leq 0.16 \mu\text{g/kg}$ ) levels of DMNA in the predialysis blood samples. The remaining four had no detectable DMNA. Of these nine patients, eight had blood collected 15 minutes after starting dialysis and

immediately after dialysis. Two samples, from patient 1 fifteen minutes after starting dialysis and from patient 2 after dialysis, unfortunately were not collected (Table 2). Each of these patients had undergone dialysis against a dialysate that had DMNA present (Table 2). The DMNA blood levels in these patients were noticeably raised from their respective predialysis blood levels.

A single-factor analysis of variance with repeated measurements showed a significant difference among the three time periods. Further pairwise comparisons using the Newmann-Keuls method showed no significant difference between intradialysis and postdialysis levels, but both were significantly (at the .05 level) elevated above the predialysis levels.

Using linear correlation, no significant relationship was observed between DMNA levels in the dialysate and those in patients' blood before the dialysis began. The dialysate levels were, however, positively correlated with blood levels during and after dialysis (correlation coefficients of .84 and .85, respectively, with each significant at the .05 level).

Because the results strongly suggested that DMNA was being generated in certain dialysis water treatment systems (a preliminary evaluation [Table 1] suggested that the presence of a deionizer in the water purification system was the critical element), an activated carbon filter (which probably adsorbs a precursor of DMNA)<sup>5</sup> was placed before and/or UV light (which decomposes DMNA) was placed after the deionizer. Following this procedure, little or no DMNA was detected in the final dialysate.

No DMNA was present in dialysate from all 11 units in which a mixed-bed deionizer was either absent or modified by carbon filter or UV light. Dimethylnitrosamine was present in all five units in which an unmodified mixed-bed deionizer was present. Using Fisher's exact test, a significant relationship ( $P < .002$ ) was demonstrated between the appearance of DMNA in dialysate and the presence of an unmodified mixed-bed deionizer. Of six patients from group 1 who had blood specimens drawn 15 minutes after starting dialysis and after dialysis, only one had a measurable

DMNA level (only  $0.08 \mu\text{g/L}$ ). Of nine patients from group 2 who had blood samples drawn 15 minutes after starting dialysis and after dialysis, all nine had DMNA blood level greater than  $0.14 \mu\text{g/L}$  (Table 2).

## COMMENT

Dimethylnitrosamine has been shown to be a potent carcinogen in animals.<sup>6</sup> The target organ for cancer is variable, depending on the animal species, the frequency and the size of the dose, and the route of administration. Thus, in the rat, repeated small oral doses of DMNA mixed in food produced malignant primary hepatic tumors,<sup>7</sup> whereas a single large dose resulted in renal cancer.<sup>8</sup> Dimethylnitrosamine is rapidly metabolized by the liver to give a series of dealkylation compounds, which are the ultimate carcinogenic species.<sup>9</sup> The demonstration that this carcinogen is generated by water treatment and then found in the patients' blood at a level many times above that of predialysis levels is of great concern, particularly since the peripheral blood level of DMNA may represent only a small portion of the more extensively metabolized parent compound.

This study was difficult to perform and complete. The highest priority was given to finding the source of DMNA in unit 13 and eliminating it. Changes were made in the system by nursing staff and maintenance workers in an attempt to eliminate the DMNA. Deionizers were changed more frequently, new sand was put into the filter, a new reverse-osmosis membrane was installed, the system was back-flushed, rubber fittings were replaced by plastic ones, and the entire plumbing system was chemically sterilized. These changes accounted, in part, for fluctuations in the dialysate DMNA levels (Table 2). Finally, an activated carbon filter was installed before the deionizers. This resulted in a dramatic decrease in the DMNA level, with elimination of substantial levels of DMNA from dialysate and blood.

We wish to draw special attention to the increase in group 2 blood DMNA levels 15 minutes after starting dialysis and after dialysis compared with group 1. Despite constraints imposed by limited data, the

appearance of DMNA in dialysate and subsequently in patients' blood 15 minutes after starting dialysis and after dialysis was clearly related to the use of a mixed-bed deionizer that was unmodified by either an activated carbon filter before or a UV light after the deionizer. Although the predialysis DMNA levels in blood were slightly higher in group 2 when compared with group 1 (0.05 v 0.10  $\mu\text{g/kg}$ , respectively), they were still within the range found in normal subjects. It is not surprising that the predialysis DMNA blood levels were relatively low even in group 2, since DMNA is rapidly metabolized in vivo.

Further support for the deionizer generation of DMNA was found in the following two observations. First, a dialysis unit from group 2 (unit 13, Table 1) had high levels of DMNA (range, 5 to 32  $\mu\text{g/L}$ ); however, after insertion of an activated carbon filter immediately before the deionizer, no DMNA was detected. Second, the postdeionizer water from a previously DMNA-negative dialysis unit (unit 11, group 1) recently became strongly positive for DMNA (similar to group 2). Similarly, the 15-minute intradialysis blood level also became strongly positive for DMNA. The presence of DMNA was directly associated with the temporary removal of the spent activated carbon filter. When a regenerated carbon filter was replaced, the levels of DMNA in the deionized water dropped to those found previously in group 1.

Because water often contains many impurities, deionizers, inter alia, are used in chemical and food processing, laboratory purification of water, treatment of drinking water with high salt content, and in dialysis treatment systems. Low levels (0.01 to 0.34  $\mu\text{g/L}$ ) of DMNA of unknown origin have been reported in water from deionizers. In most water treatment systems, deionizers are the mixed-bed type consisting of strong cation and anion resins. The cation

resin removes most ionic species, such as iron, aluminum, calcium, magnesium, potassium, sodium, and other ions, from dilute solution. It also effectively removes nitrogenous bases, including amines, from water. The anion resin removes ionic species, such as carbonate, sulfate, nitrate, nitrite, chloride, acetate, fluoride, and others.

What, then, is the mechanism for DMNA formation in the deionizer? The presence of trace DMNA as organic impurities in the deionizer (at the time of manufacture) and the concentration of preformed DMNA on the resin have both been excluded by other researchers.<sup>5</sup>

In previous studies, DMNA was formed when tap water was passed through a strong anion-exchange resin column alone, suggesting that the quaternary ammonium compound containing the trimethylamine group that is present in the anion resin may serve as the amine precursor for nitrosamine formation. Another possibility is that bacteria with the potential metabolic capacity to promote DMNA formation may contaminate the resin, since contamination of mixed-bed resins by microorganisms is not uncommon.

If the capacity to promote DMNA formation resides in the resin of the deionizer, as postulated, why does the placement of an activated carbon filter upstream from the deionizer prevent DMNA formation in the deionizer? This point has not yet been completely clarified, but it is probable that the activated carbon filter removes some unidentified volatile nitrosating species that is essential for nitrosamine formation in the deionizer, since the same result can be obtained by degassing or boiling the water.<sup>4</sup>

The analysis of DMNA in blood has been reported.<sup>10</sup> There does not appear to be controversy over the ability to detect and quantify DMNA in water or biological materials. There appears to be concern, however, for

artificial formation of DMNA during the analytical procedure and for cross-contamination from other samples and standards. Particular attention was paid to these points during all analyses, sample handling, and storage. Water blanks were run with every set of blood samples distilled. Residual chlorine was not found in the water samples.

The finding that a carcinogenic compound was being produced after water treatment with a deionizer system justifies more detailed investigation and reevaluation of both the purification modules used in dialysis systems and the water standards guidelines.

This investigation was supported by grant CA 26571 from the National Cancer Institute.

Steven Gorman, Walter Kimoto, PhD, Judith Pascale Foster, and Robert Gates, MS, assisted with this study.

Caution should be exercised in handling nitrosamines, since they are potential carcinogens.

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